REMARKS

Reconsideration and allowance of the application are respectfully requested in light of the following remarks.

Claims 2-6, 8-12, 29-33, 39-43, 55, 56, 60 and 62 are pending in this application.

The present application relates to a method of resensitizing non P-gp/non MRP multiple drug resistant cancer cells to treatment with chemotherapeutic agents to which cancer cells have developed resistance.

The present application further relates to a method for resensitizing BCRP-mediated multiple drug resistant cancer cells to treatment with chemotherapeutic agents to which cancer cells have developed resistance.

The present application additionally relates to a method of reversing BCRP or other non P-gp/non MRP resistance to chemotherapeutic agents in a mammal.

Additionally the present application relates to a method of inhibiting efflux of a chemotherapeutic agent in a mammal.

In particular the methods of the present invention comprise administration of a chemosensitizing reversal agent and a chemotherapeutic agent.

The chemosensitizing compounds resensitize cancer cells BCRP or other non-P-gp/non MRP multiple drug resistance to the effects of chemotherapeutic agents.

The chemosensitizing compounds identified in the invention do not have the cytotoxic effects of chemotherapeutic agents. In particular, the chemosensitizing compounds identified in the invention can resensitize cells to the cytotoxic effects of chemotherapeutic drugs and may be further used in combination with chemotherapeutic agents.

The Examiner has rejected claims 2-6, 8, 9-12, 29-33, 39-43, 55, 56, 60 and 62 under 35 USC 112 first paragraph, because the specification, while being enabling for the particular chemotherapeutic agents herein disclosed in the instant claims 3, 5 or 55 for example does not reasonably provide enablement for the employment of any chemotherapeutic agents and any chemosensitizing reversal agents employed in the instant rejected claimed method.

The Examiner has further rejected claims 2-6, 8, 9-12, 29-33, 39-43, 55, 56, 60 and 62 wherein the instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation.

In response, applicant respectfully traverse the rejection of claims 2-6, 8, 9-12, 29-33, 39-43, 55, 56, 60 and 62 because applicants believe the specification is enabling within the meaning of 35 USC 112. Applicants believe that the specification including the described testing procedures in the present application enable the invention within the meaning of 35 USC 112 and provide clear guidance.

As presented in the specification on page 4, lines 33-35, and page 14 lines 5-6 "A further feature of the invention is a method of distinguishing P-gp/MRP multiple drug resistance from BCRP or other non-P-gp/non MRP multiple drug resistance which comprises administration of an effective amount of a chemosensitizing reversal agent and a chemotherapeutic agent to which cancer cells are resistant and measuring cancer cell survival."

As presented in the specification on page 5, lines 7-11, "A further aspect of the invention is a method of distinguishing P-gp/MRP multiple drug resistance from BCRP or other non-P-gp/non MRP multiple drug resistance which comprises administration of an effective amount of a chemosensitizing reversal agent and a chemotherapeutic agent to which the cancer cells are multiple drug resistant and measuring chemotherapeutic agent accumulations in the cell."

As presented in the specification on page 5, lines 12-16, "An additional feature of the invention is a method of determining the presence and magnitude of cancer cell BCRP or other non P-gp/non MRP resistance in cancer cells exhibiting such resistance which comprises administration of an effective amount of a chemosensitizing reversal agent and chemotherapeutic agents to resistant cancer cells from humans and measuring cancer cell survival."

As an illustration of testing procedures and test results are those described in the specification and in Table 14 on page 33 where the test results of resensitizing S1-M1-3.2 Human Colon Cancer Cells to Mitoxantrone and Toxicity of Fumitremorgin A, B and C and Diketopiperazines against S1-M1-3.2 are presented. The concentration of compounds, Fumitremorgin A, B, C and examples of Formula (I) at the doses described (μM) are toxic doses which kill more than 20% of the cells. When the same compounds are given with Mitoxantrone where the concentration of compound that kills 50% of the cells is less than the toxic doses which identifies these compounds as resensitizing the cells to the chemotherapeutic effects of Mitoxantrone.

To further illustrate the above, the ability of FTC to resensitize S1-M1-3.2 cells to mitoxantrone is shown in Table 7 where cells were incubated for three days with the indicated doses of FTC alone or in combination with 3.2 μM mitoxantrone. Cell survival is estimated using the SRB assay described on page 18 of the specification.

No toxicity of FTC alone was observed in the dose range tested (0.1-80μM). However, in combination with mitoxantrone, 50% of the cells were killed with 0.35 μM of the drug.

In further illustration of the test procedures and results with further chemotherapeutic agents the Examiner's attention is drawn to Table 10, in the specification on pages 27-28, where multiple antitumor agents are tested with the chemosensitizing compound FTC in multiple cell lines wherein the test data show an increase in reversal activity with mitoxantrone(93 fold), doxorubicin(26 fold) and topotecan(24 fold).

Applicants believe they have provided sufficient working examples.

Based on the foregoing, it is respectfully submitted that the present application contains more than sufficient description and guidance to enable the skilled artisan to carry out the method set forth in the claims without undue experimentation. Accordingly, withdrawal of the section 112 first paragraph rejection is respectfully urged.

Additionally, applicants believe that the terms chemotherapeutic agent and chemosensitizing reversal agent are not purely functional distinction. In fact, a chemosensitizing reversal agent

is not the same as a chemotherapeutic agent for chemosensitizing agents do not have the chemotherapeutic activity but do resensitize chemotherapeutic agents to multiple drug resistant cancer cells.

Applicants believe the rejection can be withdrawn.
Applicant respectfully requests the Examiner to withdraw the Section 112 rejection.

The Examiner has rejected claims 2, 4-6, 8-10, 29-31, and 39-41 under 35 USC 102(b) as being anticipated by Abe et al. (Br. J. Cancer, 1995, 72, page 418-423).

Applicants respectfully traverse the 35 USC 102(b) rejection. Abe has two MRP expressing cell lines called T98G and IN500. Abe further uses an MDR-1(P-gp) expressing cell line called CCF-STTG-1 and an additional cell line IN-157 which does not express P-gp or MRP. The IN-157 is not a multiple drug resistant cell line, but is a control for the drug resistant cells. Abe looks for chemosensitizing agents for P-gp and MRP multiple drug resistant cells which is different from the instant invention which is BCRP or other non P-gp-nonMRP resistance.

The Abe reference evaluates the ability of various compounds to resensitize drug resistant cells that overexpress MDR-1 or MRP. The instant invention focuses on cell lines which develop resistance by pathways (non-P-gp-non-MRP), specifically BCRP. The Abe reference has a different type of resistance which is P-gp or MRP multiple drug resistance. In contrast, the instant invention focuses on non-P-gp-non MRP resistance.

In addition, it is the applicants view that the Abe reference does not inherently distinguish P-gp/MRP multiple drug resistance from BCRP or other non-P-gp/non MRP because the Abe reference evaluates the ability of various compounds to resensitize drug resistant cells that overexpress MDR-1 or MRP. The present invention however, focuses on cell lines which develop resistance by pathways (non-P-gp-non-MRP), specifically BCRP. The Abe reference has a different type of resistance which is P-gp or MRP multiple drug resistance. In contrast, the instant invention focuses on non-P-gp-non MRP resistance.

In addition, it is the applicants view that the Abe reference does not inherently distinguish P-gp/MRP multiple drug resistance from BCRP or other non-P-gp/non MRP because the Abe

reference evaluates the ability of various compounds to resensitize drug resistant cells that overexpress MDR-1 or MRP. The present invention however, focuses on cell lines which develop resistance by pathways (non-P-gp-non-MRP), specifically BCRP. The Abe reference has a different type of resistance which is P-gp or MRP multiple drug resistance. In contrast, the instant invention focuses on non-P-gp-non MRP resistance.

In particular, verapamil is shown by Abe to resensitize P-gp and MRP multidrug resistant cells to chemotherapeutic agents. However in the instant application in particular as shown in table 6 verapamil had no effect on the cells S1-M1-3.2 described in our application.

Based on the foregoing, applicant respectfully requests the Examiner to withdraw the Section 102b rejection.

The Examiner has rejected claims 2, 4-6, 8-10, 29-31 and 39-41 under 35 USC 102(b) as being anticipated by Greenberger et al (Oncology Research, Vo. 8, No. 5, pp 207-218).

As described by the Examiner, Greenberger et al. discloses chemosensitizing agent that restored sensitivity to drugs in the multidrug resistance (MRD) phenotype in cell lines that overexpress P-glycoprotein. Such agents resensitized drug-resistant tumors to vinblastine or doxorubicin in an ascitic or solid tumor model respectively.

Applicants respectfully traverse the 35 USC 102(b) rejection. Greenberger et al. describe a chemosensitizing agent for P-gp (MDR1) mediated MDR while in contrast the instant invention describes sensitized cells that do not express P-gp or MRP, i.e. exhibit non P-gp /non MRP MDR.

The instant invention distinguishes between P-gp/MRP multiple drug resistance and non P-gp and non MRP multiple drug resistance.

The cell line of the instant invention expresses neither P-gp nor MRP multiple drug resistance but expresses BCRP and is therefore distinct from the art.

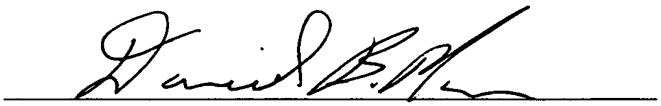
It is the applicants view that the the Greenberger reference does not inherently distinguish P-gp/MRP multiple drug resistance from BCRP or other non-P-gp/non MRP because the

reference only identifies a compound that resensitizes P-gp multiple drug resistance: while the present invention however, describes a method for distinguishing between P-gp/MRP multiple drug resistance and non P-gp and non MRP multiple drug resistance.

Applicant respectfully requests the Examiner to withdraw the Section 102b rejection.

In conclusion, applicants respectfully request that the Examiner enter the amendment, reconsider the rejections in light of the remarks herein, amendments to the claims, and allow the application. Favorable treatment is earnestly solicited.

Respectfully submitted,



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